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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,759	05/30/2001	David S. Terman		8812

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EXAMINER	
HUMPHREY, DAVID HAROLD	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,759	TERMAN, DAVID S.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-10,26,29 and 30* is/are pending in the application.

4a) Of the above claim(s) *8-10,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 7 and 26, filed on July 22, 2005 is acknowledged. Applicant's election of species, gangliosides, is also acknowledged.

   Claims 7-10, 26, 29, and 30 are pending.

   Claims 8-10, 29, and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

   Claims 7 and 26 are examined on the merits to the extent they read on the elected species, gangliosides.

Specification

2. The specification is objected to for the following reasons: it does not contain a Cross-Reference to Related Applications in the first paragraph (see Content of Specification 37 CFR 1.78 and MPEP § 201.11) and the Sequence Listing is not identical to the submitted CRF sequence information (see 37 CFR 1.821-1.825 and MPEP §§ 2421-2431). The requirement for a sequence listing applies to all sequences disclosed in a given application, whether the sequences are claimed or not. See MPEP § 2421.02.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. For example, on pages 438 and 439, there are editorial comments that should be deleted from the text. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

3. Claims 7 and 26 are objected to because of the following informalities: claim 7 has an extra period after "proteoglycolipids" that should be deleted and claim 26 contains an extra "and" that should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 7 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The claims do not include how the presence of tumor-associated lipids in claim 7 or of tumor-associated antigens in claim 26 is going to generate a tumoricidal immunocyte population with inactivated or deleted receptors and adaptor proteins, respectively; hence the method steps do not correlate with the preamble. And while all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is practiced. The method steps should at least include reagents necessary for the assay, a detection step in which the reaction products are quantitated or visualized and a correlation step describing how the results of the assay allows the determination of for example, the prognosis of a disease. While it is clear from claim 7 that tumor-associated lipids are contacted with an

immunocyte containing an inactivated or deleted receptor, the claims do not provide how the combination will result in a tumoricidal immunocyte population. Contact does not seem to positively elicit a population of tumoricidal immunocytes. It is unclear how a tumoricidal population of immunocytes is generated by the contact of these two. Likewise, is the scenario for claim 26. Therefore, the claims are indefinite because they merely recite a use without all the required active and positive steps delimiting how the use is actually practiced.

b. Claims 7 and 26 are narrative in form and replete with indefinite and functional or operational language. The term "allowing" is vague and indefinite. In claim 7, it is unclear if the tumor-associated lipids are actively administered to the immunocytes or are produced by the mammal's tumor. The recitation of "tumor-associated lipids" is indefinite. It is unclear if tumor-associated lipids are present in higher concentrations on tumor cells than on non-tumor cells or do not exist at all on non-tumor cells. Likewise, claim 26 is vague and indefinite for the recitation "allowing a tumor-associated antigen..." It is unclear what the method allows the said antigen to do.

c. The phrase, "receptors for immunosuppressive ...gangliosides are inactivated or deleted" in claim 7, is vague and indefinite. It is unclear how the receptor could be deleted in vivo as the claim recites. Since the claims encompass all mammals, deletion of a receptor in vivo reads on the generation of transgenic humans. For the reasons cited above, the phrase, "the adaptor proteins ...are deleted or functionally deactivated" in claim 26, is also vague and indefinite.

As written, one of skill in the art would not be able to determine the metes and bounds of the claimed invention.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 7 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner has interpreted the claims to read on a method for generating a tumoricidal immunocyte population in vivo in a mammal comprising inactivating or deleting receptors for immunosuppressive gangliosides or adaptor proteins that inhibit T cell activation. Then, the immunocytes are contacted with tumor-associated lipids or tumor-associated antigens. Claim 7 reads on inhibition of ganglioside receptors and claim 26 reads on the inactivation of adaptor proteins. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art.

The instant specification does not provide sufficient guidance to enable methods involving the inactivation of ganglioside receptors and the inactivation adaptor proteins which inhibit T cell activation. The state of the art does not support Applicant's claimed method invention.

The determination that "undue experimentation" would have been needed to make and use the claimed inventions is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the factual considerations, see In re Wands, 8 USPQ2nd 1400. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of one of ordinary skill;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The existence of working examples; and
8. The quantity of experimentation needed to make or use the invention on the content of the disclosure.

The instant specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as

claimed. Those of skill in the prior art would recognize the unpredictable role of tumor-related gangliosides in the inhibition of the cellular immune response. For example, Birkle et al. (Biochimie 85: 455-463 (2003)) teach that the mechanisms of immunosuppression caused by tumor shed ganglisodes are most likely multiple and remain to be fully elucidated, see page 460, bottom right column, last paragraph. Furthermore, Birkle et al. teach that tumor-derived gangliosides inhibit multiple steps in the cellular immune response in vitro including the activity of helper T cells, the cytotoxicity of natural killer cells, antigen- and mitogen-stimulated T and B cells, see page 460, right column, second paragraph. Tumor-derived gangliosides also block the production of TNFα as well as antigen presentation by human monocytes, see page 460, right column, second paragraph. Therefore, gangliosides may physiologically function to coordinate the activation of multiple receptors, see page 461, left column, first paragraph. From these studies, one of skill in the art would recognize that there are multiple receptors for tumor-derived gangliosides. Therefore, the effects of tumor-derived gangliosides are not limited to interactions with immunosuppressive receptors. In addition, tumor-derived gangliosides have also been shown to bind directly to the immunocyte-stimulating cytokine, IL-2, in the fluid surrounding the cancer tissue. The result is competitive inhibition of IL-2 from binding to IL-2 receptors and interference with intercellular signaling since IL-2 secretion and binding is central to T cell proliferative response.

Therefore, tumor-derived gangliosides could still have an immunosuppressive effect in the absence of ganglioside receptors by binding to

IL-2 in the extracellular fluid surrounding the cancer tissue. A third mechanism for tumor-derived ganglioside inhibition of immunocytes is by direct incorporation of the tumor-derived gangliosides into the membrane of target cells. Since the disclosure in no way addresses these critical issues, or provides objective evidence or working examples, one of ordinary skill in the art would not have a reasonable expectation of success to practice the claimed invention. Lack of working examples is given added weight in cases involving an unpredictable art such as the immunosuppressive mechanisms of gangliosides.

Claim 26 recites a method for producing a tumoricidal T cell population in vivo in a mammal in which adaptor proteins that inhibit T cell activation by tumor associated antigens are deleted or functionally inactivated. A tumor-associated antigen is subsequently administered to the T cells resulting in a highly activated T cell population. The specification discloses the inactivation or deletion of Src like adaptor protein (SLAP), prior to exposure to a tumor-associated antigen, will lead to the activation of T cells, page 203, section 57. Those of skill in the prior art would recognize the unpredictable nature of T cell responses when adaptor proteins are inactivated or deleted. Griffiths et al. (Science 293:2260-2263 (2001)) teach the function role of SLAP (also known as Fyb) has remained controversial because protein overexpression studies have produced contradictory results, see page 2260, middle column, lines 8-13. Griffiths et al. teach that SLAP is a critical positive regulator of T cell activation and function. SLAP -/- T cells are defective in TCR-mediated activation, proliferation, and cytokine production, see page 2261, right column, last paragraph. In vivo, SLAP

-/- chimeric mice display impaired immunity to T cell dependent antigens, see page 2261, right column, last paragraph. Therefore, the teachings of Griffiths et al. have shown that the inactivation of the adaptor protein, SLAP, results in a decrease of T cell activation in response to T cell dependent antigens.

Krause et al. (U.S. Pub. No.: US2002/0037286; April 3, 2000 effective filing date) disclose methods for altering T cell activation by administering activators or inhibitors of the adaptor protein, SLAP, to subjects at risk of developing an infectious disease or cancer, see page 2, paragraphs 15 and 16. Krause et al. teach that administration of SLAP inhibitors results in the inhibition of the T cell response, see page 2, paragraph 17. Both the method of Krause et al. and the claimed invention involve the inactivation of the adaptor protein, SLAP to modulate the activity of T cells. However, Krause et al. obtain inactivated T cells whereas the claimed invention produces activated, tumoricidal T cells.

Therefore, one of ordinary skill in the art would not expect to generate a tumoricidal T cell population by deleting or functionally deactivating the adaptor protein, SLAP, as in the claimed invention. Further, the disclosure provides no objective evidence or working examples to lend one of ordinary skill in the art a reasonable expectation of success. Lack of working examples is given added weight in cases involving an unpredictable art as the role of adaptor proteins play in the inhibition or activation of T cells by tumor associated antigens.

In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that it would require undue experimentation to successfully practice the invention as claimed.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

David Humphrey, Ph.D.
September 30, 2005